PATENT

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Applicant :	Mueller-Hermelink, et al.	Art Unit :	1643
Serial No. :	10/579,290	Examiner :	Bristol, Lynn Anne
Filed :	05/15/06		
Title :	ADENOCARCINOMA SPECIFIC ANTIBODY SAM-6, AND USES THEREOF		

Assistant Commissioner for Patents

Washington, DC 20231

DECLARATION UNDER 37 C.F.R. §1.132

Dear Sirs:

I, Dr. Heinz Peter Vollmers, do hereby declare and state that:

1. I am a resident of Würzburg, Germany. My residence address is: Bonhoefferstrasse 19, 97078, Würzburg, Germany. I received Diploma of Science degree in Biology from the University of Tübingen in Germany. I received a Doctor of Science degree in Biology from the University of Tübingen in Germany. I received a Doctor degree in Medicine from the University of Würzburg in Germany. I received a Professor degree in Medicine from the University of Würzburg in Germany.

2. I am one of the inventors of the subject matter described and claimed in United States Patent Application Serial No. 10/579,290, filed May 15, 2006, entitled: "ADENOCARCINOMA SPECIFIC ANTIBODY SAM-6, AND USES THEREOF."

3. I am currently a professor at the University of Würzburg, Germany. My CV is attached which reflects my expertise in the fields of Immunology and Oncology. I am currently a consultant for Patrys Ltd, the assignee of the above-identified application.

4. I am familiar with the claims under consideration.

5. I have reviewed the Office Action mailed May 5, 2009, and understand that the Examiner has rejected certain claims under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description and as allegedly lacking enablement.

Antibodies and functional fragments that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3

6. I submit this Declaration to affirm that one skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and antigen binding fragments that specifically bind to a polypeptide expressed by at least one of the recited cell lines, and (i) that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3; (ii) that comprise a light chain variable region sequence at least 80% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 80% identical to SEQ ID NO:3; (iii) that comprise a light chain variable region sequence at least 85% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 85% identical to SEQ ID NO:3; (iv) that comprise a light chain variable region sequence at least 90% identical to SEQ D NO:1, and comprise a heavy chain variable region sequence at least 90% identical to SEQ ID NO:3; or (v) that comprise a light chain variable region sequence at least 95% identical to SEQ ID NO:1, and comprise a heavy chain variable region sequence at least 95% identical to SEQ ID NO:3.

7. The following are objective facts, and conclusions based upon the objective facts, in support of this Declaration:

8. The specification discloses light chain variable region amino acid sequence, SEQ ID NO:1, and heavy chain variable region amino acid sequence, SEQ ID NO:3 (sequence listing). The specification discloses that light and heavy chain variable region sequences SEQ ID NOs:1 and 3 are derived from a human antibody (Example 2). The specification also discloses the predicted sequence of all three CDRs in the variable region sequences (see, for example, page 5, lines 8-21, and page 2, lines 19-30; and the sequence listing). Thus, the skilled artisan would know the sequence of the light and heavy chain variable regions and the predicted locations of the CDRs in light and heavy chain variable regions. Furthermore, as the predicted locations of the CDRs in SEQ ID NOs:1 and 3 would be known to the skilled artisan, the skilled artisan would also have known the location of the framework regions (FRs) in SEQ ID NOs:1 and 3, as well as the D- and J-regions in SEQ ID NOs:1 and 3. Consequently, the skilled artisan would know the sequence and location of amino acid residues of SEQ ID NOs:1 and 3 that contribute to antigen binding.

9. The level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high. As evidence of the high level of knowledge and skill in the art at the time of the invention, the specification discloses the function of antibody heavy and light chain variable (e.g., CDR and FR) and constant regions (page 29, line 16, to page 30, line 14), and the role of variable region sequences, including CDRs, in antigen binding was known in the art at the time of the invention (see, for example, Immunology, Goldsby, R.A., 5th ed. W.H. Freeman, 2002). Consequently, the level of

knowledge and skill in the art concerning antibody structure and function at the time of the invention was high.

10. Because the amino acid residues of light and heavy chain variable region sequences SEQ ID NOs:1 and 3 that contribute to antigen binding would be known to one of skill in the art in view of the specification and the high level of knowledge and skill in the art concerning antibody structure and function, the skilled artisan would have known a number of antibodies and antigen binding fragments with amino acid residues of SEQ ID NOs:1 and 3 that could be substituted (i.e., would likely not destroy binding activity). Consequently, the skilled artisan would envision light chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and heavy chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.) that would have at least partial binding activity. To illustrate this point, the skilled artisan would know that an amino acid substitution, for example, a non-conservative or conservative substitution outside a CDR or FR region of SEQ ID NOs:1 or 3 would likely not destroy binding activity. Conservative substitutions within a CDR or FR region of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody or antigen binding fragment. Thus, the skilled artisan would know of a number of antibodies and antigen binding fragments comprising SEQ ID NO:1 or 3 with non-conservative or conservative substitutions located outside of a CDR or FR of SEQ ID NO:1 or 3, or conservative substitutions within a CDR or FR of SEQ ID NO:1 or 3, that likely retain at least partial binding activity.

11. Typically, about half of the amino acid residues in a given heavy or light chain variable region sequence are not within one of the three CDRs. In view of large number of amino

acids outside of the CDRs the skilled artisan would envision a number of residues outside of the CDRs that could be substituted and likely retain at least partial binding activity. Thus, the skilled artisan would readily envision antibodies and antigen binding fragments with light chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and heavy chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), that would retain at least partial binding activity without actually having to verify that the variant has at least partial binding infirmity.

12. As stated above, the skilled artisan would, in view of the guidance in the specification and knowledge of the structural function relationships of antibodies, readily envision antibodies and antigen binding fragments with light chain variable region sequences with 75% or more identity to SEQ ID NO:1 (e.g., 80%, 85%, 90%, 95%, etc.), and heavy chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.) that retain at least partial binding activity. The skilled artisan would also know of nonfunctional variants. For example, the skilled artisan knows that heavy chain variable region CDR3 appears to confer fine binding specificity, and therefore that a large number of non-conservative substitutions, insertions or deletions of heavy chain variable region CDR3 would likely result in loss of antigen binding specificity. Consequently, the skilled artisan would also know SEQ ID NOs:1 and 3 with sufficient substitutions, insertions or deletions such that the antibody or fragment would be unlikely to have binding activity.

13. The ability of the skilled artisan to envision antibodies and antigen binding fragments with light chain variable region sequences with 75% or more identity to SEQ ID NO:1

(e.g., 80%, 85%, 90%, 95%, etc.), and heavy chain variable region sequences with 75% or more identity to SEQ ID NO:3 (e.g., 80%, 85%, 90%, 95%, etc.), that would retain at least partial binding activity is further evidenced by the fact that humanizing antibodies was known at the time of the invention (see, for example, U.S. Patent No. 6,180,370). In particular, grafting non-human CDRs to human framework sequences to form an antigen binding antibody was well established at the time of the invention. Because the CDRs of a given variable region sequence could be transferred entirely from one species to another without destroying binding activity of the resultant antibody, the skilled artisan would readily envision that antibodies and antigen binding fragments could comprise CDR's of one species and fragments of another without destruction of antigen binding activity that comprise light chain variable region sequences with 75% or more identity to SEQ ID NO:1, and heavy chain variable region sequences with 75% or more identity to SEQ ID NO:3. Consequently, given that humanized antibodies retain binding and that variable region sequences can include non-identical amino acids in many positions outside of the CDRs without destroying binding activity, variants can be substantially non-identical to SEQ ID NOs:1 and 3 outside of the CDRs while retaining binding activity. The skilled artisan would therefore readily envision a number of antibodies and antigen binding fragments that vary in positions outside of the CDRs of SEQ ID NOs:1 and 3 that retain at least partial binding activity.

14. To illustrate that substitutions within CDRs are tolerated, Kipriyanov et al. (Protein Engineering 10:445 (1997)) report that a substitution of a cysteine residue by a serine within CDR3 of any antibody light chain variable did not have an adverse effect on binding affinity. Thus, the skilled artisan would know antibodies and antigen binding

fragments with a substitution of a light or heavy chain variable region CDR residue are tolerated and would not necessarily destroy binding activity. As such, one skilled in the art would know a variety of variants outside CDRs that would be predicted to bind to antigen.

15. To illustrate that substitutions within FRs can generally be tolerated, Holmes *et al.* (J. Immunol. 167:296 (2001)) report that several light chain variable region FR substitutions of an anti-lysozyme antibody did not destroy binding activity. Thus, again antibodies and antigen binding fragments with a substitution of a light or heavy chain variable region FR residue are tolerated and would not destroy binding activity.

Antibodies and functional fragments that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3, wherein the light or heavy chain variable region sequence has an insertion or deletion of one amino acid residue

16. I also submit this Declaration to affirm that one skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would be apprised of a number of antibodies and antigen binding fragments that specifically bind to a polypeptide expressed by at least one of the recited cell lines and that comprise a light chain variable region sequence at least 75% identical to SEQ ID NO:1 and a heavy chain variable region sequence at least 75% identical to SEQ ID NO:3, wherein the light or heavy chain variable region sequence has an insertion or deletion of one amino acid residue.

17. The following are objective facts, and conclusions based upon the objective facts, in support of this Declaration:

18. As stated above, the sequence of amino acid residues of light and heavy chain variable region sequences SEQ ID NOs:1 and 3 and corresponding CDRs, FRs, etc. that contribute to antigen binding would be known to one of skill in the art, and the level of knowledge and skill in the art concerning correlative antibody structure and function was high. Thus, the skilled artisan would have known antibodies and functional fragments with substitutions of SEQ ID NOs:1 and 3 that would not destroy binding activity and therefore would envision variable region sequences with 75% or more identity to SEQ ID NO:1 and 3 (e.g., 80%, 85%, 90%, 95%, etc.) with at least partial activity. In addition, an amino acid insertion or deletion of SEQ ID NOs:1 or 3 would also likely not destroy binding activity of an antibody. Insertions and deletions of amino acid residues in heavy and light chain variable regions, including CDRs, occur naturally during antibody affinity maturation (see, for example, Wilson *et al.*, J. Exp. Med. 187:59 (1998)). Thus, the skilled artisan would know with a high degree of confidence that an antibody or antigen binding fragment comprising SEQ ID NO:1 or 3 with an amino acid insertion or deletion within or outside of a CDR, would very likely retain at least partial binding activity.

19. To further corroborate that antibodies and antigen binding fragments with a light or heavy chain variable region sequence insertion or deletion can be tolerated, even within a CDR, Lantto and Ohlin (J. Biol. Chem. 277:45108 (2002)) report that single amino acid insertions or deletions of CDRs 1 and 2 of light chain variable region of an antibody were well tolerated. Thus, Wilson *et al.*, and Lantto and Ohlin corroborate that antibodies and

antigen binding fragments that comprise a light or heavy chain variable region sequence insertion or deletion even within a CDR can be tolerated.

Producing Antibodies and functional fragments having Binding Activity

20. I further submit this Declaration to affirm that one skilled in the art, in view of the guidance of the specification and the knowledge and skill in the art at the time of the invention, could produce antibodies and antigen binding fragments having a sequence at least 75% identical to SEQ ID NO:1 or SEQ ID NO:3 that specifically binds to a polypeptide expressed by at least one of the recited cell lines without undue experimentation.

21. The following are objective facts, and conclusions based upon the objective facts, in support of this Declaration:

22. Producing recombinant proteins was routine in the art at the time of the invention. In addition, the specification discloses routine assays for identifying antibodies that bind to the recited cell types, as well as cell proliferation/apoptosis assays (Examples 1 and 3 to 5). Methods of producing variants including conservative amino acid substitutions at pre-determined locations are disclosed in the specification (page 34, line 24, to page 36, line 26), including conservative amino acid substitutions. Thus, variants of antibodies and antigen binding fragments could be produced at the time of the invention without undue experimentation.

23. In addition to producing antibodies and antigen binding fragments without undue experimentation, binding activity could be verified without undue experimentation in view of the guidance in the specification and knowledge in the art at the time of the

invention. For example, the specification discloses routine assays for identifying antibodies and fragments that specifically bind to at least one of the recited cell lines, as well as cell proliferation and apoptosis assays. Methods of identifying variant antibodies and antigen binding fragments that have binding activity, without undue experimentation, were also known in the art and are also disclosed in the specification. In particular, methods for measuring binding to the recited carcinoma cell lines, and methods for ascertaining cell proliferation and apoptosis, are disclosed in the specification (Examples 1 and 3 to 6). Additional methods for producing and screening antibodies and fragments for binding activity were known in the art at the time of the invention (see, for example, A Practical Guide to Monoclonal Antibodies by J. Eryl Liddell (Author), A. Cryer (Author), John Wiley & Sons, 1991).

24. Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily produce antibodies and antigen binding fragments with a light and heavy chain variable region sequence at least 75% identical to SEQ ID NO:1 and 3, that retain at least partial binding activity without undue experimentation.

Antibodies and antigen binding fragments comprising CDR1, CDR2 and CDR3 of SEQ ID NO:1 and CDR1, CDR2 and CDR3 of SEQ ID NO:3

25. I additionally submit this Declaration to affirm that the skilled artisan, in view of the guidance of the specification and the knowledge and skill in the art concerning antibody structure and function at the time of the invention, would envision a number of antibodies and antigen binding fragments that include CDRs 1, 2, and 3 of SEQ ID NO:1 and CDRs 1, 2 and 3 of SEQ ID NO:3 that retain at least partial activity.

26. The following are objective facts, and conclusions based upon the objective facts, in support of this Declaration:

27. As discussed, the level of knowledge and skill in the art concerning antibody structure and function at the time of the invention was high, and the specification discloses the function of antibody light and heavy chain variable regions, CDR and FR regions, and the role of variable region sequences, including CDRs and FRs, in antigen binding, all of which were known to the skilled artisan at the time of the invention.

28. Furthermore, the specification discloses the predicted sequence of all 6 CDRs in SEQ ID NO:1 and SEQ ID NO:3. In view of the foregoing, the skilled artisan would know the predicted location and identity of the majority of amino acid residues of SEQ ID NO:1 and SEQ ID NO:3 that contribute to antigen binding. Consequently, the skilled artisan would know amino acids of SEQ ID NO:1 and 3 that would be amenable to substitution, such as for example, a non-conservative or conservative substitution outside a CDR. Thus, the skilled artisan would have known with a high degree of confidence that an antibody or antigen binding fragment with a non-conservative or conservative substitution located outside of a CDR of SEQ ID NO:1 or SEQ ID NO:3 is very likely to retain at least partial binding activity.

29. In addition, as also discussed in detail above, humanizing and humanized antibodies were known to the skilled artisan at the time of the invention. In particular, grafting non-human CDRs to human framework sequences and combining it with constant region sequences was well established at the time of the invention. Because all CDRs of a given variable region sequence could be transferred from one mammalian species to another without destroying binding activity of the resultant humanized antibody, the skilled

artisan could readily envision variants of SEQ ID NO:1 that retain the CDRs of SEQ ID NO:1 and variants of SEQ ID NO:3 that retain the CDRs of SEQ ID NO:3 that have binding activity. Furthermore, in view of the fact that about 50% of the amino acids of SEQ ID NO:1 and 3 are outside of the CDRs, sequence variants that likely retain at least partial activity would be readily envisioned by the skilled artisan. Moreover, given that humanized antibodies retain binding, variable region sequences can include non-identical amino acids in many positions outside of the CDRs and yet still retain at least partial binding activity, and therefore can be substantially non-identical to SEQ ID NO:1 and 3 outside of the CDRs.

30. In sum, the skilled artisan would readily envision a number of antibodies and antigen binding fragments that include CDR1, CDR2 and CDR3 of SEQ ID NO:1 and CDR1, CDR2 and CDR3 of SEQ ID NO:3 that retain at least partial activity, without actually having to analyze particular variants for building activity.

31. Finally, for the reasons discussed in detail above, antibodies or antigen binding fragments that include the three CDRs of SEQ ID NO:1 or the three CDRs of SEQ ID NO:3 that retain at least partial activity could be produced and the activity verified without undue experimentation, in view of the guidance in the specification and knowledge in the art at the time of the invention for producing recombinant proteins, identifying antibodies and antigen binding fragments that bind to at least one of the recited cell types, as well as cell proliferation/apoptosis assays. Thus, one skilled in the art could readily produce antibodies and antigen binding fragments that include CDRs 1, 2 and 3 of SEQ ID NO:1 and CDRs 1, 2 and 3 of SEQ ID NO:3 that bind at least one of the recited cell lines without undue experimentation.

32. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 28.09.09

Heinz Peter Vollmers, Ph.D